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Synthesis, structure and catalytic activity of new ferrocenyl-containing secondary alcohols derived from L-proline

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General information
NMR experiments were carried out on Brucker-Avance 400 MHz spectrometer in $CDCl_3$ using TMS as an internal reference.
Specific rotation was determined by Kruss P-8000 instrument for chloroform solutions in 5 cm cuvette.
For column chromatography silica gel (0.04 – 0.063 mm) was used.
Determinations of enantiomeric excess were carried out by HPLC on Shimadzu L20 device with a refractometric detector RID-20A. The column Lux i-Amilose-15 um 100x4,6 mm was used, eluent – a 99:1 mixture of heptane and *i*-PrOH. For an adjusting of the column racemic substances were synthesized.
For high resolution mass spectrometry micrOTOF instrument was used.

N-Benzyloxycarbonyl-L-proline ethyl ester **2** was synthesized from L-proline with 87% yield according to a published procedure[S1].
^{1}H NMR (mixture of *Z*- and *E*-amides, *Z* : *E* = 1 : 1; $CDCl_3$, 400 MHz, δ, ppm): 1.14 (t, ^{3}J = 7.13 Hz, O-CH_2C*H_3*, *Z* or *E*), 1.26 (t, ^{3}J = 7.13 Hz, O-CH_2C*H_3*, *E* or *Z*), 1.94 (m, 3 H, pyrr), 2.20 (m, 1 H, pyrr), 3.50 (m, 1 H, pyrr), 3.62 (m, 1 H, pyrr), 4.05 (m, O-C*H_2*CH_3, *Z* or *E*), 4.20 (m, 1 H, O-C*H_2*CH_3, *E* or *Z*), 4.32 (dd, ^{3}J = 3.9 Hz, N-C*H*, *Z* or *E*), 4.37 (dd, ^{3}J = 3.6 Hz, N-C*H*, *E* or *Z*), 5.12 (m, 2 H, C*H_2*-Ph), 7.33 (m, 5 H, Ph); *cf.*[S1]

[(S)-N-Methylpyrrolidine-2-yl]diphenylmethanol **1c** was synthesized from L-proline with 75% yield according to a published procedure[S2].
^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.65 (m, 3 H, pyrr), 1.80 (s, 3 H, NMe), 1.89 (m, 1 H, pyrr), 2.42 (m, 1 H, pyrr), 3.09 (m, 1 H, pyrr), 3.61 (dd, 1 H, ^{3}J = 4.4 Hz, ^{3}J = 9.5 Hz, N-C*H*), 4.70 (br, 1 H, O*H*), 7.12 (m, 2 H, Ph), 7.25 (m, 4 H, Ph), 7.53 (m, 2 H, Ph), 7.63 (m, 2 H, Ph); *cf.*[S2]
^{13}C{1H} NMR ($CDCl_3$, 100 MHz, δ, ppm): 24.16, 30.01, 43.09, 59.26, 72.06, 77.56, 125.54, 125.58, 126.23, 126.25, 128.11, 128.14, 146.83, 148.37.

[(S)-N-Benzyloxycarbonylpyrrolidine-2-yl] ferrocenyl ketone **3**
A solution of ferrocenylmagnesium bromide prepared as described above from bromoferrocene (1.66 g) was diluted with ether (10 ml) and added for 1 h by drops with a vigorous stirring to an ice-cooled solution of *N*-benzyloxycarbonyl-L-proline ethyl ester **2** (1.39 g, 5.0 mmol) in ether (30 ml). The reaction mixture was stirred for additional 4 h. A ruby precipitate was formed. Then water (5 ml) was added, wherein the precipitate was dissolved. The organic layer was separated and water layer was extracted with ethyl acetate. The combined organic solutions were dried over Na_2SO_4 and solvent was removed on rotor evaporator. The residue was subjected to column chromatography. The first yellow-orange band was eluted with 100:1 mixture of benzene and acetonitrile and discarded. Elution with 10:1 mixture of benzene and acetonitrile gave an intensive red second band which was collected and solvent from eluate was removed on rotor evaporator. The residue was recrystallized from hexane (150 ml). 0.63 g; (30%) of ketone **3** was obtained as red crystalline substance, m. p. 131-132°C.
^{1}H NMR (mixture of *Z*- and *E*-amides, *major* : *minor* = 2 : 1; $CDCl_3$, 400 MHz, δ, ppm): 1.86 (m, 2 H, pyrr), 1.99 (m, pyrr, *major*), 2.08 (m, pyrr, *minor*), 2.27 (m, 1 H, pyrr), 3.59 (m, 2 H, pyrr), 4.13 (s, C_5H_5, *minor*), 4.39 (s, C_5H_5, *major*), 4.50 (m, C_5H_4, *major* + *minor*), 4.55 (m, C_5H_4, *major*), 4.64 (m, C_5H_4, *minor*), 4.67 (m, C_5H_4, *major*), 4.83 (m, C_5H_4, *minor*), 4.87 (dd, ^{3}J = 9.0 Hz, ^{3}J = 3.2 Hz, N-C*H*, *minor*), 4.93 (m, C_5H_4, *major*), 4.99 (dd, ^{3}J = 9.2 Hz, ^{3}J = 2.9 Hz, N-C*H*, *major*), 5.06 (d, ^{2}J = 12.5 Hz, C*H*HPh, *minor*), 5.16 (d, ^{2}J = 12.5 Hz, C*H*HPh, *major*), 5.23 (d, ^{2}J = 12.5 Hz, C*H*HPh, *major*), 5.28 (d, ^{2}J = 12.5 Hz, C*H*HPh, *minor*).^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, δ, ppm): 23.07, 23.83, 30.56, 31.90, 46.67, 47.27, 62.77, 63.08, 66.89, 69.12, 69.28, 69.31, 69.67, 69.86, 70.29, 72.25, 72.32, 72.41, 76.12, 116.17, 127.77, 127.90, 127.97, 128.21, 128.51, 136.87, 136.99, 154.58, 154.92, 201.90, 202.06.
ESI-HRMS: calculated for $C_{23}H_{23}FeNO_3^+$ (M^+) 417.1022; found 417.1019.
$[\alpha]_D^{20}$: +312 deg/g (c 5×10^{-3} g/ml, $CHCl_3$).

[(S)-N-Methylpyrrolidine-2-yl]ferrocenylmethanol **6a**,**b**

To a solution of ketone **3** (0.25 g, 0.6 mmol) in a mixture of ether and THF (20 ml each) in argon purge, lithium aluminium hydride (0.11 g; 3.0 mmol) was added in one portion with stirring. The reaction mixture was refluxed for 3 h, then was cooled to 0°C, and water (0.11 ml) was added by drops. Then 15% NaOH (0.11 ml) and water (0.34 ml) were added subsequently. The precipitate was filtered off and washed with ether. The combined filtrates were dried over Na_2SO_4 and the solvent was removed on rotor evaporator. The residue was purified by chromatography in a short column. Benzyl alcohol was eluted with petroleum ether – ethyl acetate 1:1 mixture and discarded. Then an elution with 2:2:1 mixture of petroleum ether, ethyl acetate and triethylamine gave a mixture of diastereomeric alcohols **6a** and **6b** (3:1 - determined by ^{1}H NMR). Their separation was carried out using a long column (l = 25 cm) with 10:1:1 mixture of petroleum ether, ethyl acetate and triethylamine as eluent. Small sequenced portions of eluate were collected and checked with TLC. Portions containing only fast-moving compound were combined and evaporated. Hexane was added to remove traces of triethylamine and again evaporated. A major product, [(*S*)-*N*-Methylhyrrolidine-2-yl]-(*S*)-ferrocenylmethanol **6a** (0.102 g, 57%) was obtained as an orange solid, mp 64-67°C. From portions containing only second compound, [(*S*)-*N*-methylhyrrolidine-2-yl]-(*R*)-ferrocenylmethanol **6b** (0.031 g, 17%) was obtained as orange solid, mp 96-99°C.

[(S)-N-Methylhyrrolidine-2-yl]-(S)-ferrocenylmethanol **6a**:

^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.45 (m, 1 H, pyrr), 1.62 (m, 2 H, pyrr), 1.79 (m, 1 H, pyrr), 2.27 (m, 2 H, pyrr), 2.38 (s, 3 H, NMe), 3.09 (m, 1 H, N-C*H*), 3.13 (br, 1 H, O*H*), 4.10 (m, 3 H, C_5H_4), 4.19 (s, 5 H, C_5H_5), 4.34 (m, 1 H, C_5H_4), 4.56 (d, ^{3}J = 2.9 Hz, 1 H, Fc-C*H*).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, δ, ppm): 23.22, 24.63, 40.38, 57.73, 66.34, 66.48, 67.49, 67.60, 67.99, 68.77, 70.97, 89.50.

ESI-HRMS: calculated for $C_{16}H_{22}FeNO^+$ (MH^+) 300.1045; found 300.1038.

$[\alpha]_D^{20}$: –52.8 deg/g (c 4×10^{-3} g/ml, $CHCl_3$).

[(S)-N-Methylhyrrolidine-2-yl]-(R)-ferrocenylmethanol **6b**:

^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.67 (m, 3 H, pyrr), 1.80 (m, 1 H, pyrr), 2.30 (m, 1 H, pyrr), 2.32 (s, 3 H, OMe), 2.44 (m, 1 H, pyrr), 3.05 (m, 1 H, N-C*H*), 3.45 (br, 1 H, O*H*), 4.12 (m, 3 H, C_5H_4), 4.17 (d, J = 5.2 Hz, 1 H, Fc-C*H*), 4.19 (s, 5 H, C_5H_5), 4.29 (m, 1 H, C_5H_4).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, δ, ppm): 24.33, 29.62, 43.88, 58.04, 65.71, 67.11, 67.42, 67.77, 68.67, 71.31, 72.96, 92.59.

ESI-HRMS: calculated for $C_{16}H_{22}FeNO^+$ (MH^+) 300.1045; found 300.1040.

$[\alpha]_D^{20}$: –49.8 deg/g (c 4×10^{-3} g/ml, $CHCl_3$).

General procedure for the enantioselective alkylation of benzaldehyde using pyrrollidinylmethanol as catalyst

A solution of benzaldehyde (92 μl, 0.0955 g, 0.9 mmol) and chiral pyrrolidinylmetanol (0.018 mmol, 2 mol. %) in a mixture of hexane (3 ml) and toluene (2.5 ml) was refluxed in argon purge for 20 min and then was cooled to 0°C. Diethylzinc in hexane (1 M solution, 2 ml) was added with cooling, and the mixture was stirred at 0°C for additional 24 h. To quench the reaction, 1 M HCl (10 ml) was added. The mixture was extracted with dichloromethane, the extract was dried over Na_2SO_4, and the solvent was removed on rotor evaporator. The residue was subjected to column chromatography using dichloromethane as eluent. After elution of unreacted benzaldehyde, portions which contain the main product was collected and evaporated. 1-Phenylpropan-1-ol was obtained as a colorless oil with 50-70% yield.

^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.91 (t, ^{3}J = 7.4 Hz, 3 H, CH_2CH_3), 1.78 (m, 2 H, CH_2CH_3), 1.94 (m, 1 H, O*H*), 4.58 (m, 1 H, C*H*), 7.30 (m, 5 H, Ph).

References

[S1] Y. Takeuchi, A. Yamada, T. Suzuki and T. Koizumi, *Tetrahedron*, 1996, **52**, 225–232.
[S2] K. Soai, A. Ookawa, T. Kaba and K. Ogawa, *J. Am. Chem. Soc.*, 1987, **109**, 7111–7115.

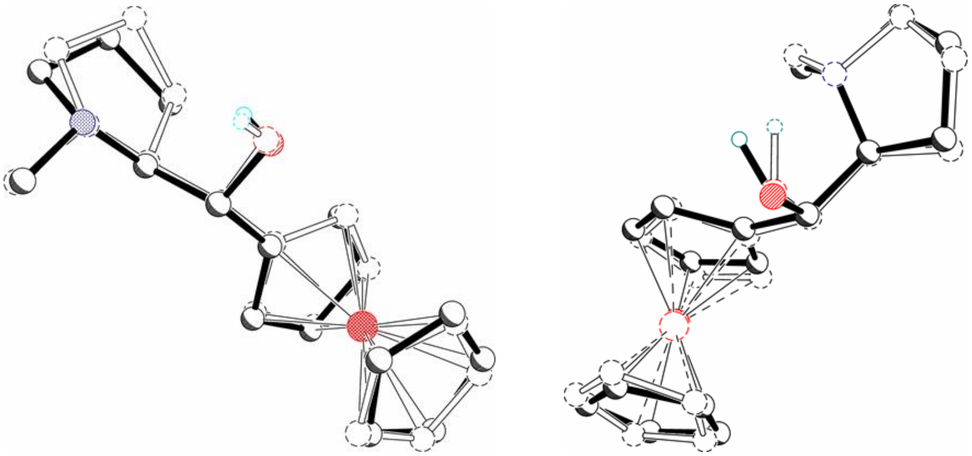

Figure S1. Orthogonal fitting diagrams for independent molecules in **6a** (left) and **6b** (right).

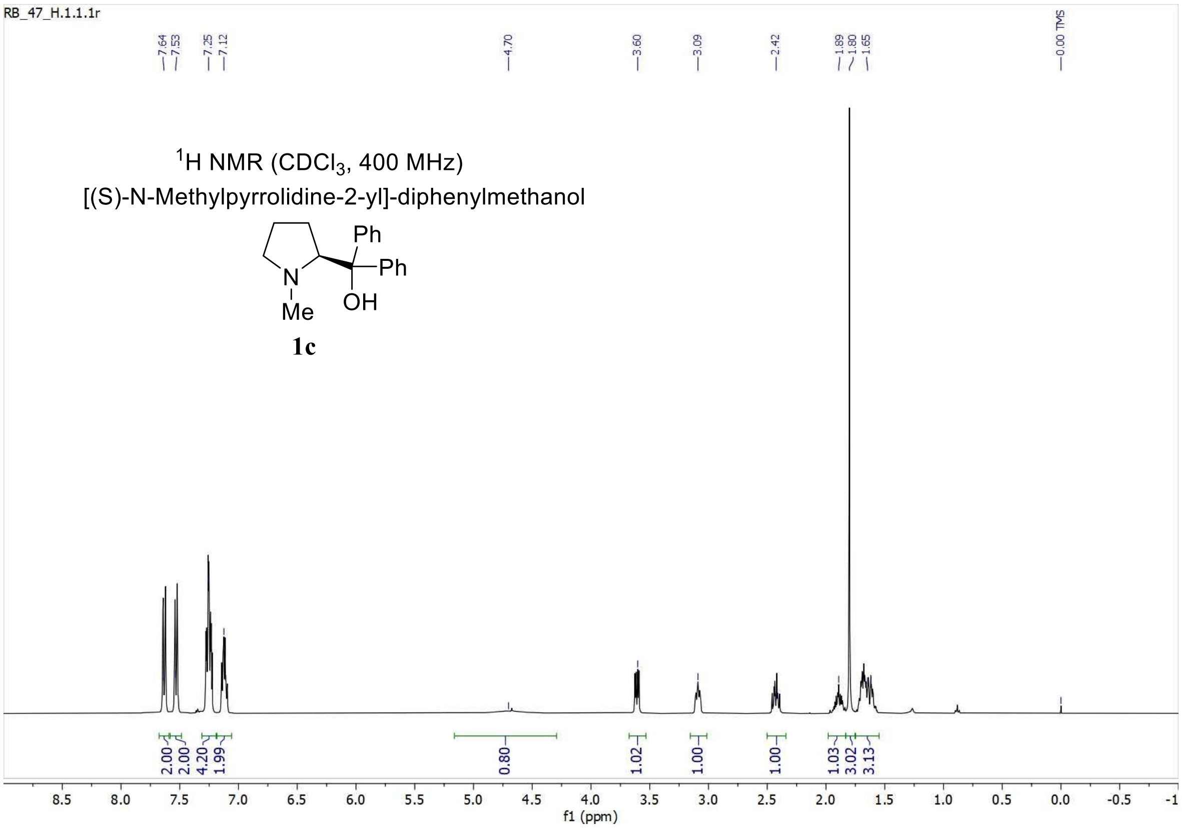

Figure S2. ^{1}H NMR Spectrum of [(*S*)-*N*-Methylpyrrolidine-2-yl]diphenylmethanol (**1c**).

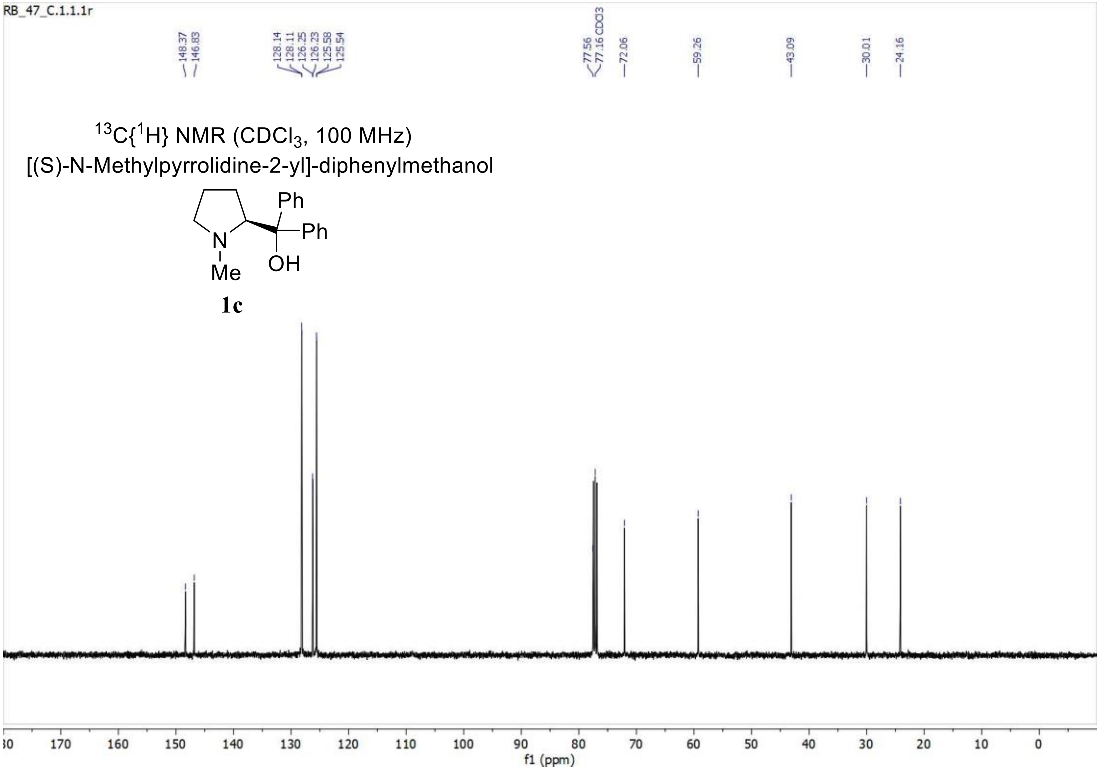

Figure S3. ^{13}C{^{1}H} NMR Spectrum of [(*S*)-*N*-Methylpyrrolidine-2-yl]diphenylmethanol (**1c**).

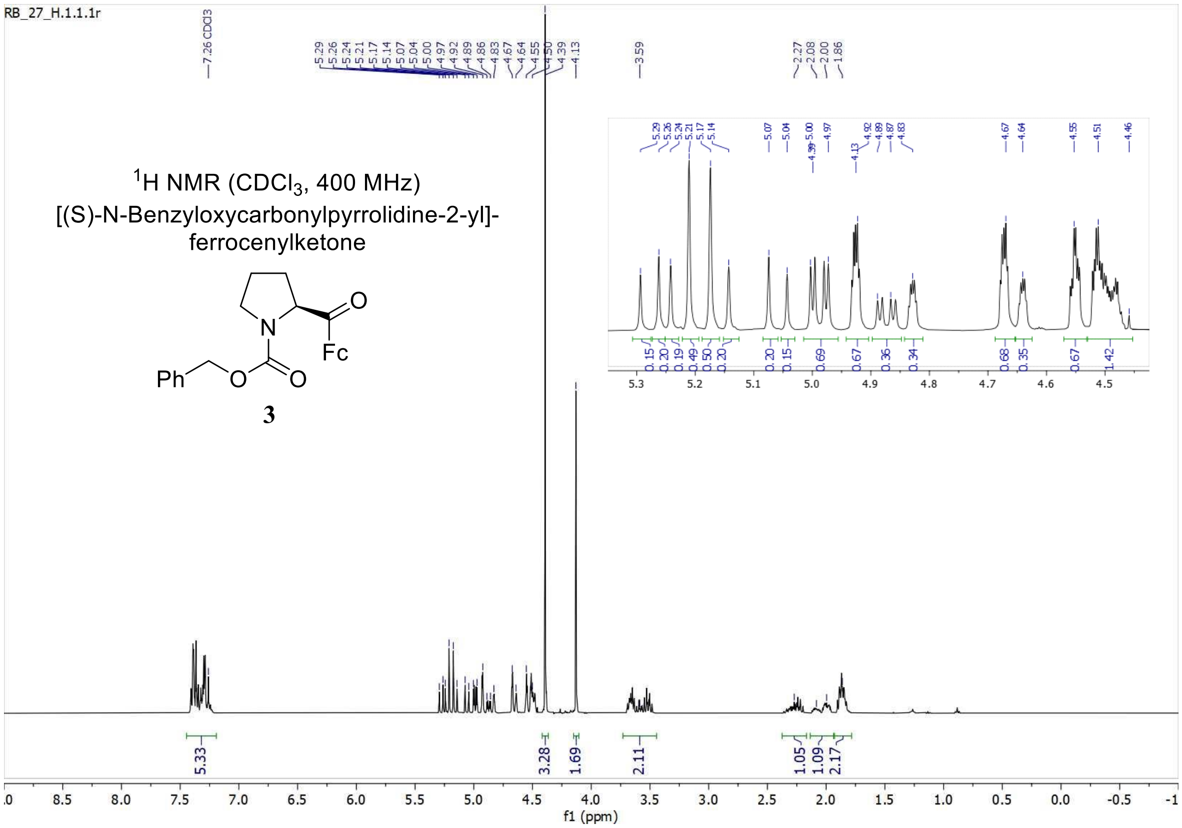

Figure S4. ^{1}H NMR Spectrum of [(*S*)-*N*-Benzyloxycarbonylpyrrolidine-2-yl] ferrocenyl ketone (**3**).

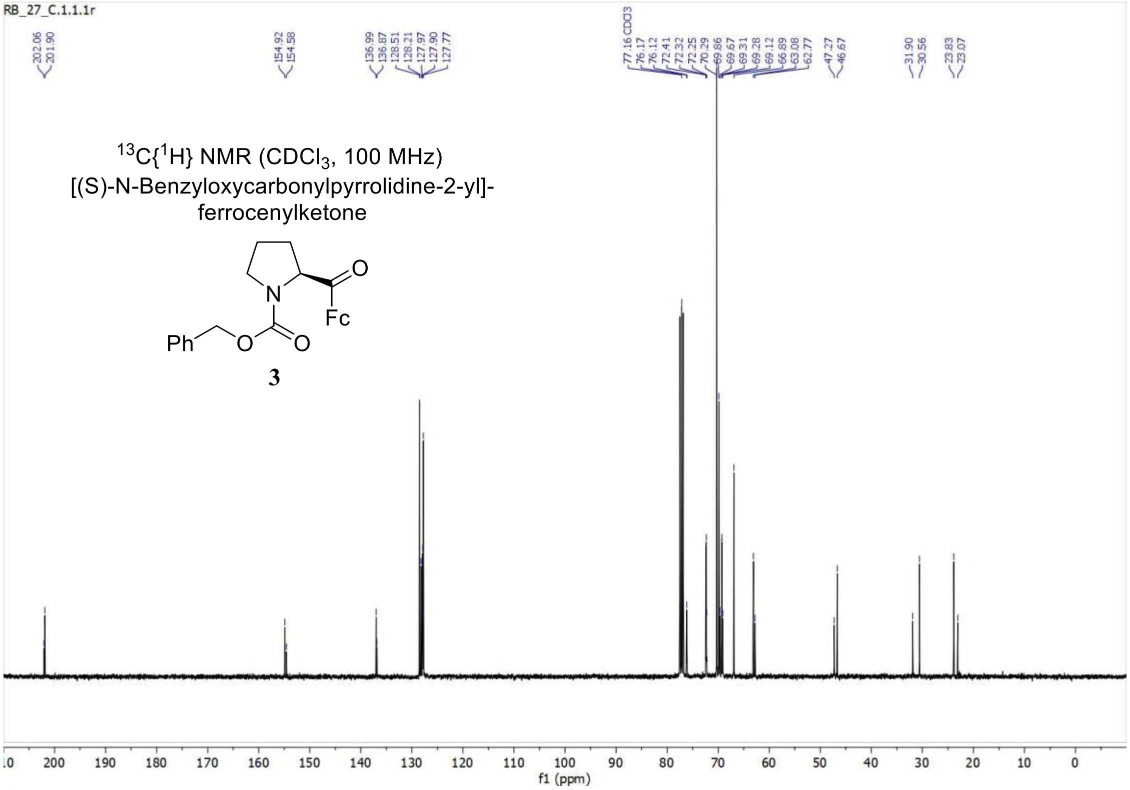

Figure S5. ^{13}C{^{1}H} NMR Spectrum of [(*S*)-*N*-Benzyloxycarbonylpyrrolidine-2-yl] ferrocenyl ketone (**3**).

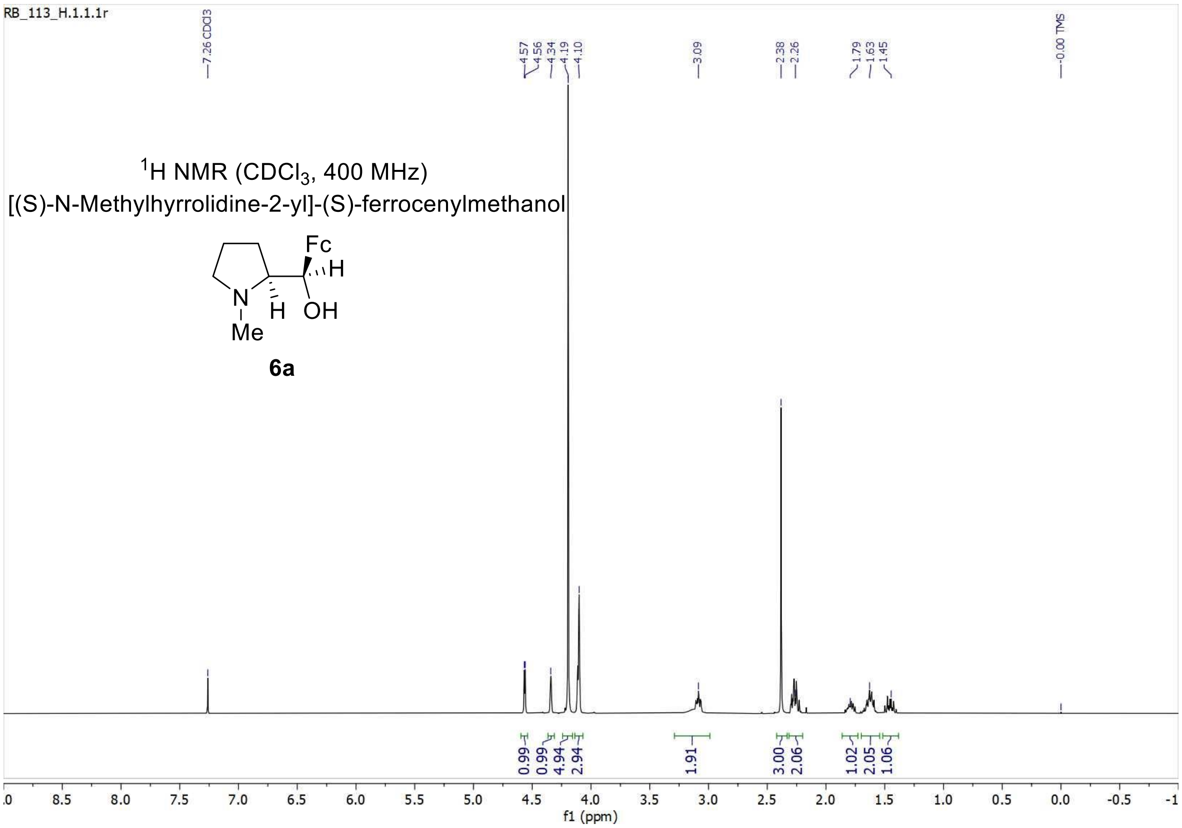

Figure S6. ^{1}H NMR Spectrum of [(*S*)-*N*-Methylpyrrolidine-2-yl]-(*S*)-ferrocenylmethanol (**6a**).

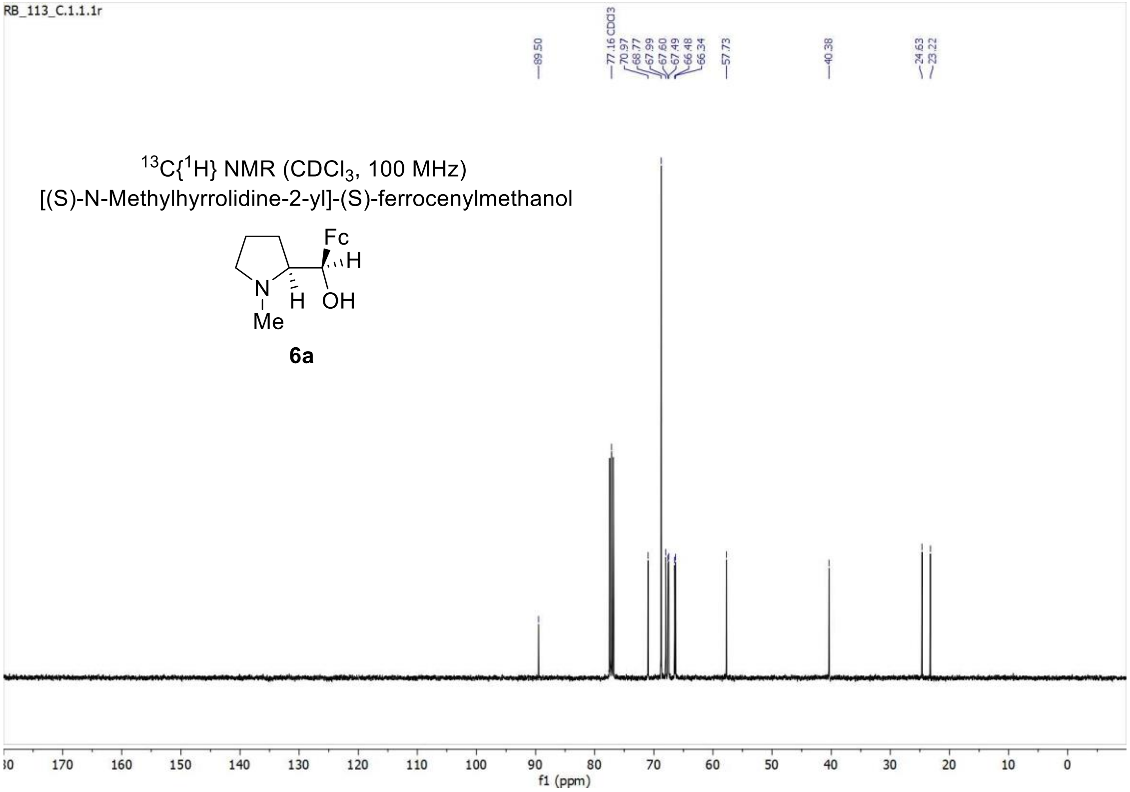

Figure S7. ^{13}C{^{1}H} NMR Spectrum of [(*S*)-*N*-Methylhyrrolidine-2-yl]-(*S*)-ferrocenylmethanol (**6a**).

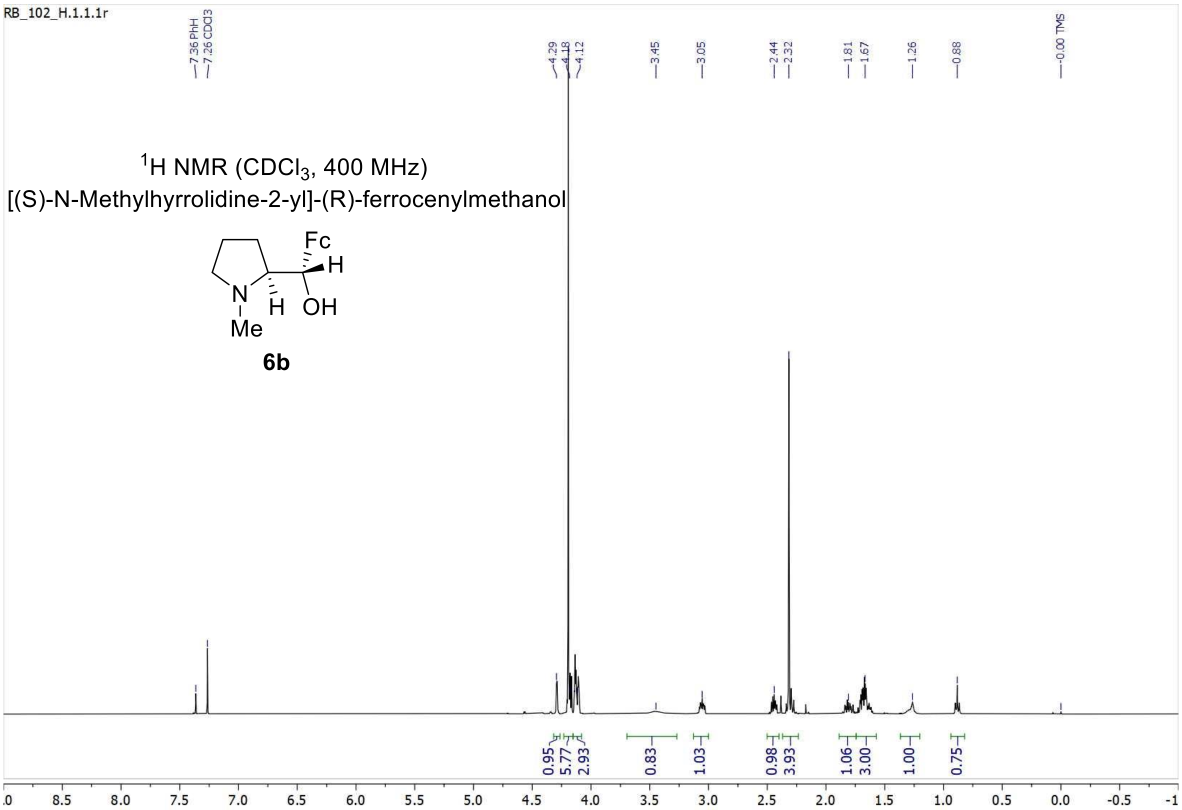

Figure S8. ^{1}H NMR Spectrum of [(*S*)-*N*-Methylhyrrolidine-2-yl]-(*R)*-ferrocenylmethanol (**6b**).

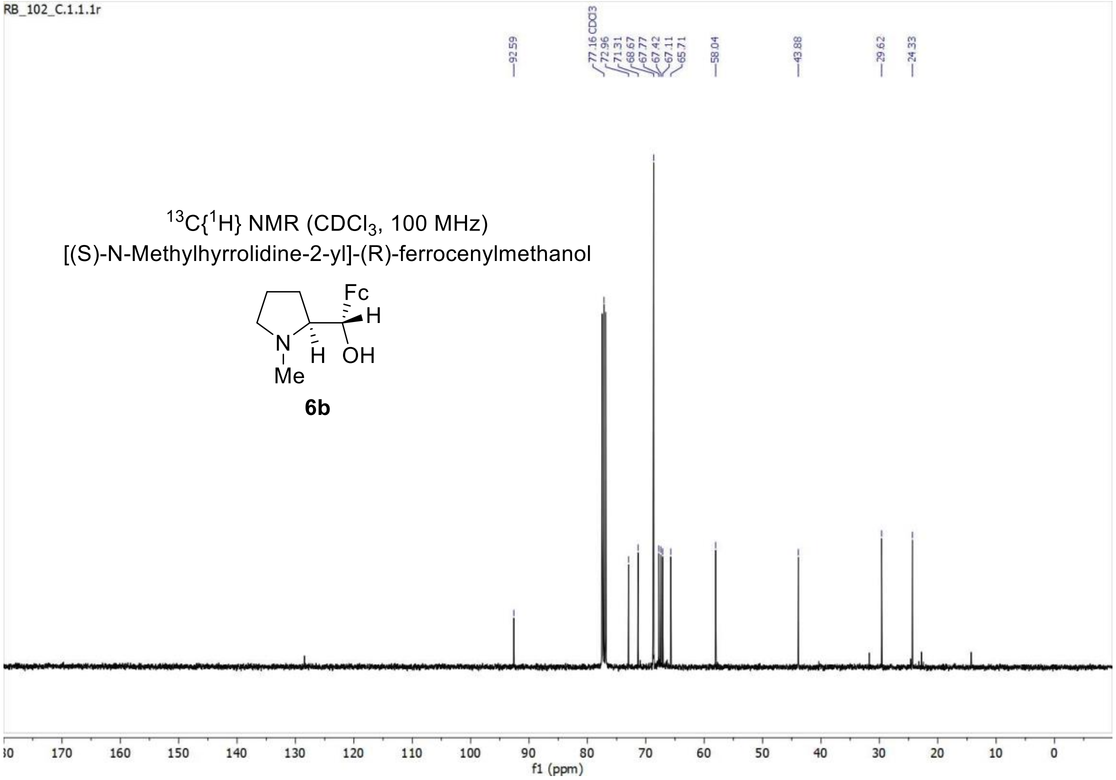

Figure S9. ^{13}C{^{1}H} NMR Spectrum of [(*S*)-*N*-Methylhyrrolidine-2-yl]-(*R*)-ferrocenylmethanol (**6b**).